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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/500,512	02/09/2000	Richard A. E. Clark	001.00251	6713

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EXAMINER	
KIM, VICKIE Y	
ART UNIT	PAPER NUMBER
1614	12

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/500,512	Applicant(s) CLARK ET AL.	
	Examiner Vickie Kim	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *26-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Response to Arguments

1. Applicant's arguments, see paper No.10, filed Jan. 18, 2002, with respect to the rejection(s)of claim(s) 1-25 and 33-34 under 103 for obviousness over US patent 5330974(Pines) in view of Gallit et al(abstract, 1997) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Brown et al(1993) and Mosesson et al(1966).

Status of Application

2. Claims 1-34 are pending.

3. The elected claims 1-25 and 33-34 are presented for the examination.

4. The non-elected claims 26-32 are withdrawn from consideration.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-25 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al (US 5935850) in view of Brown et al(1993) and Mosesson et al(1966).

Claims are drawn to a method of enhancing fibroblast migration by contacting the wound site with fibrinogen processed by precipitating plasma with glycine.

Brown et al teach about fibroblast migration where Brown suggests the enhanced fibroblast migration achieved by extensive clotting of said fibrinogen took place in vivo, see abstract. Brown's teaching is supported by measuring factor XIII activity and is tested with contacting highly purified fibrinogen(3mg/ml) that has >95 % of clottability, thrombin and calcium, see page 274," Fibrinogen purification". Brown teaches that highly purified fibrinogen is obtained when the clottability is >98%, where several plasma proteins are separated during the purification process,see figure 2 and column 1 at page 277. Brown also teaches that fibroblast migration is critical factor for the wound healing process wherein fibrinogen clotting(fibrin gel) is gradually replaced by granulation tissue and later by collagenous tissue that is deginated by "scar tissue" , see page 273, 2nd column. It is noted that formation of scar tissue is conventionally known as an initial step of wound healing process. Brown also teaches other factors regulating cell migration such as growth factors, see page 273. Furthermore, Brown teaches that fibroblast migration is maximal at the concentration of 3mg/ml, see figure 3 at page 278.

Applicant's claims differ in that they require the source of fibrinogen that should be obtained by the precipitation of plasma with glycine, Applicant's claims also require the contact of fibrinogen into the wound site to induce the said migration.

However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify Brown' teaching to include a further teaching of Clark et al and Mosesson because Mosesson and Clark et al together remedy the deficiency of Brown et al.

Clark et al teach model for cell migration and its use during wound healing, see column 1, lines 8-13. Clark utilizes in vivo model to study fibroblast cell migration induced by fibrinogen into the wound site during wound healing. I*n vivo* model, Clark uses fibrinogen(3mg/ml, >95% clottable) by contacting wound site to induce cell migration, see columns 7-8 and example 1.

Although Brown's teaching about the cell migration using fibrinogen having the concentration 3mg/ml and the concentration >95% at least) has been tested by *in-vitro* study, any skilled artisan would readily have been motivated to apply the said fibrinogen into the wound site to improve the wound healing when Brown et al is taked in view of Clark et al.

Mosesson et al teach a method for the preparation of highly purified human fibrinogen having a clottability of about 98% via repeated precipitation of plasma with glycine(starting materials).

Even though, it is not mentioned explicitly about the sources and preparation of fibrinogen in the Brown or Clark et al, when Brown is taken in view of Clark and Mosesson, One would have been motivated to use fibrinogen obtained by the preparation taught in Mosesson's because it is clearly advantageous to use highly purified fibrinogen to maximize the effectiveness as suggested by these cited references(supra).

As to the claims 2-25 and 33-34, all the critical elements required by the instant claims are taught by or obvious over the cited references. For instance, temperature (i.e. 2-5°) , the concentration of glycine(e.g. 2.1M), the pH of solution(e.g. about 7-8),

see pages 2830-2832. Mosesson et al teach reprecipitation with glycine to increase clottability more than 97% and conditions required for processing such precipitation. For instance, the reprecipitation in a buffer, the addition of ammonium sulfate, lipid-proteins, see pages 2833-2834.

Thus, one would have been motivated to use fibrinogen that has been prepared by the precipitation of plasma with glycine because the said preparation including additional purification via repeated precipitation allows the fibrinogen to increase its clottability more than about >95%, preferably > 98% which in turn, would maximize fibroblast migration when it is contacted into wound site in vivo. One would have been motivated to make such modification with reasonable expectation of success because the teaching of each reference together(Brown in view of Mosesson and Clark) provides all the necessary information that suggests the positive outcomes(Clark and Brown) proven via *in vivo and in vitro* studies and teaches the sources for highly purified material such as fibrinogen (Mosesson). Since the clottability of fibrinogen(by purification via repeated precipitations) is critical factor for fibroblast migration and heavy clotting would enhance the said migration into the wound site so that one would have been motivated to perform the test without undue burden where the minor modifications required in such test would be conventional and considered to be well within the level of the artisan having ordinary skills.

The minor variations including the selection of optimal environment and steps in order to determine the most effective treatment is well within the skilled level of artisan having ordinary skill in the art, and is obvious.

Conclusion

7. No claim is allowed.

8. This is 2nd Non-final rejection.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vickie Kim whose telephone number is 703-305-1675. The examiner can normally be reached on Tuesday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on 703-308-4725. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-3165 for regular communications and 703-746-3165 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Vickie Kim,
Patent examiner
July 24, 2003
Art unit 1614